# Etiology & Pathogenesis of AKI

By

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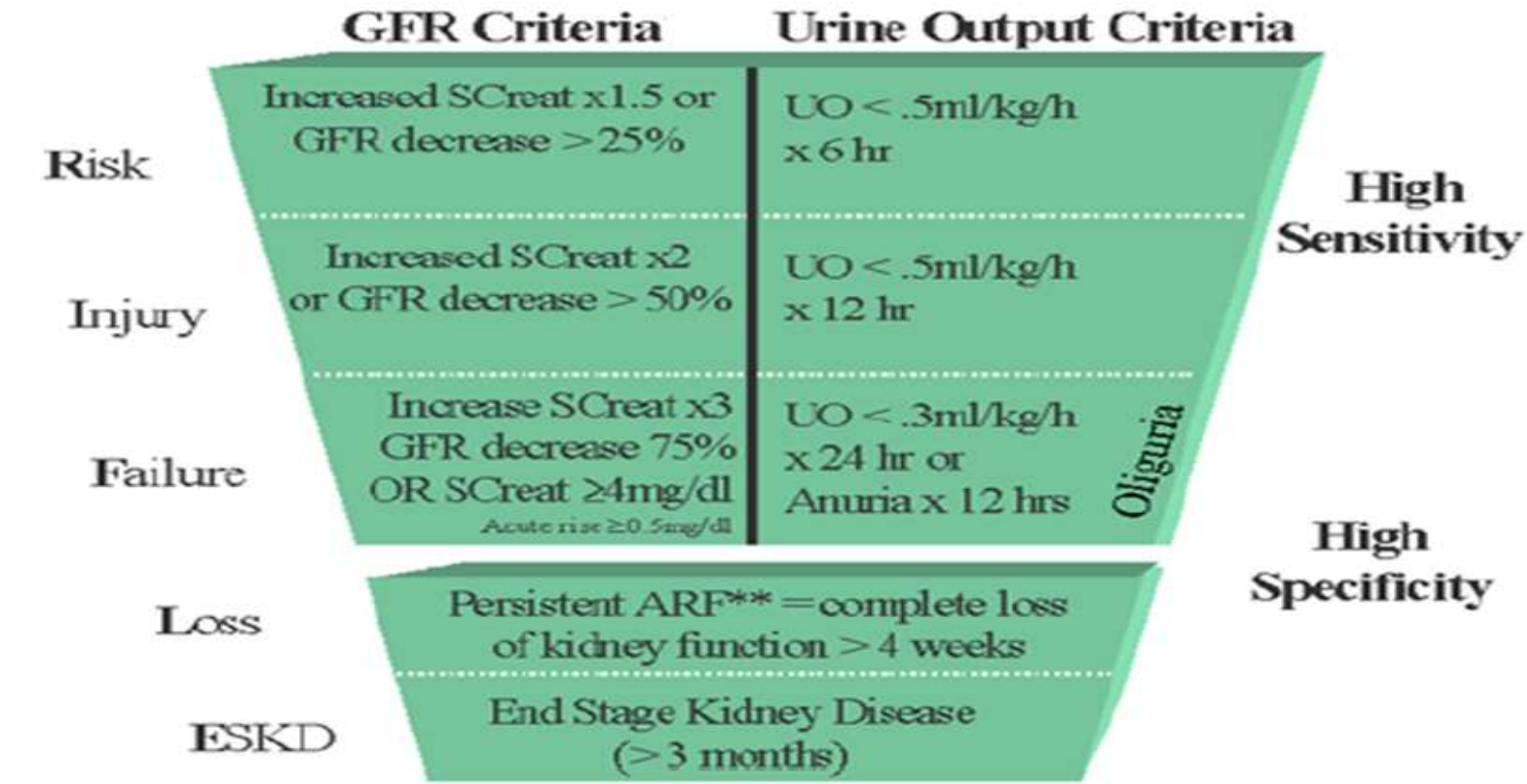
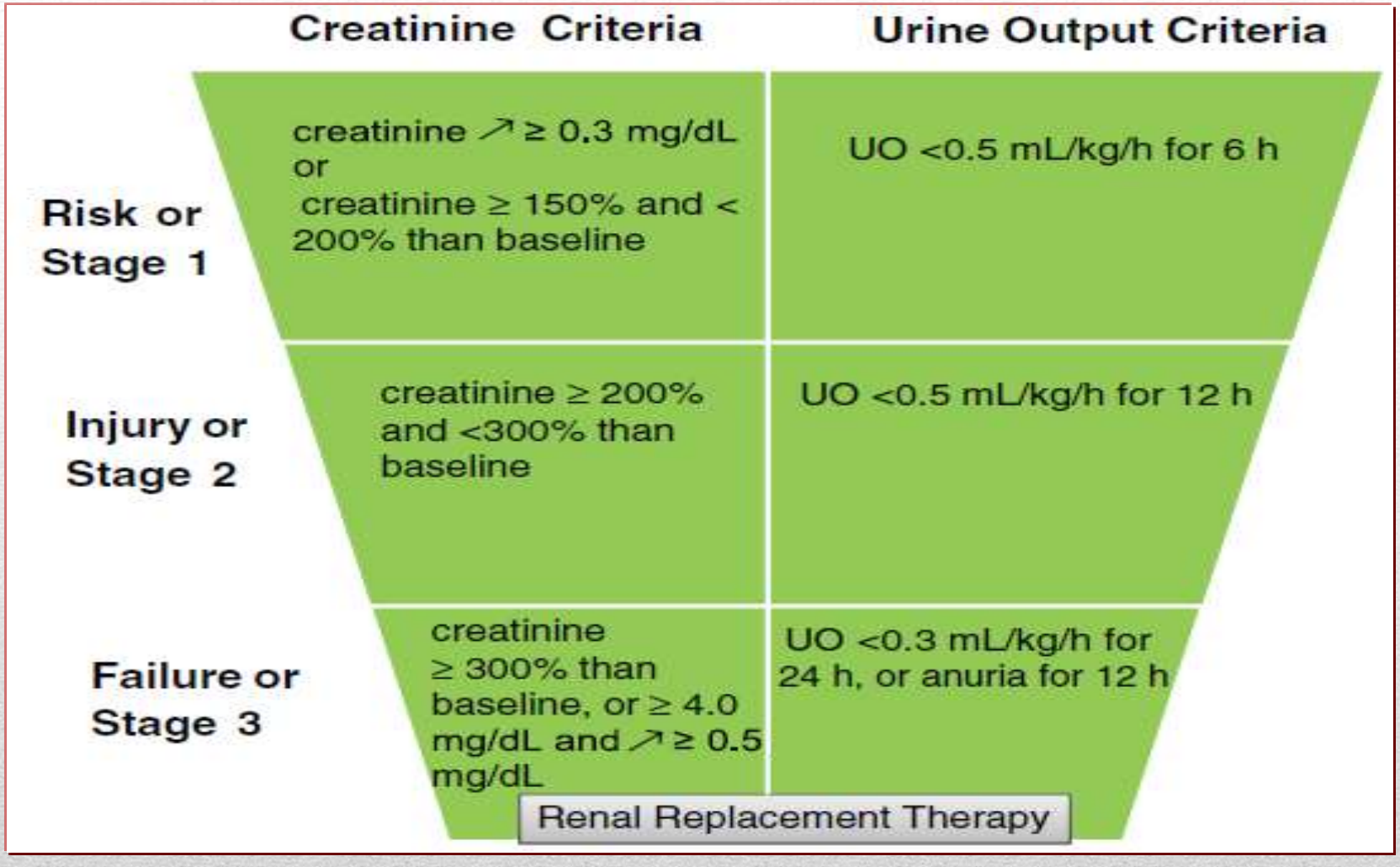
# Definition

Abrupt decline in GFR sufficient to decrease the elimination of nitrogenous waste products (urea and creatinine) and other uremic toxins

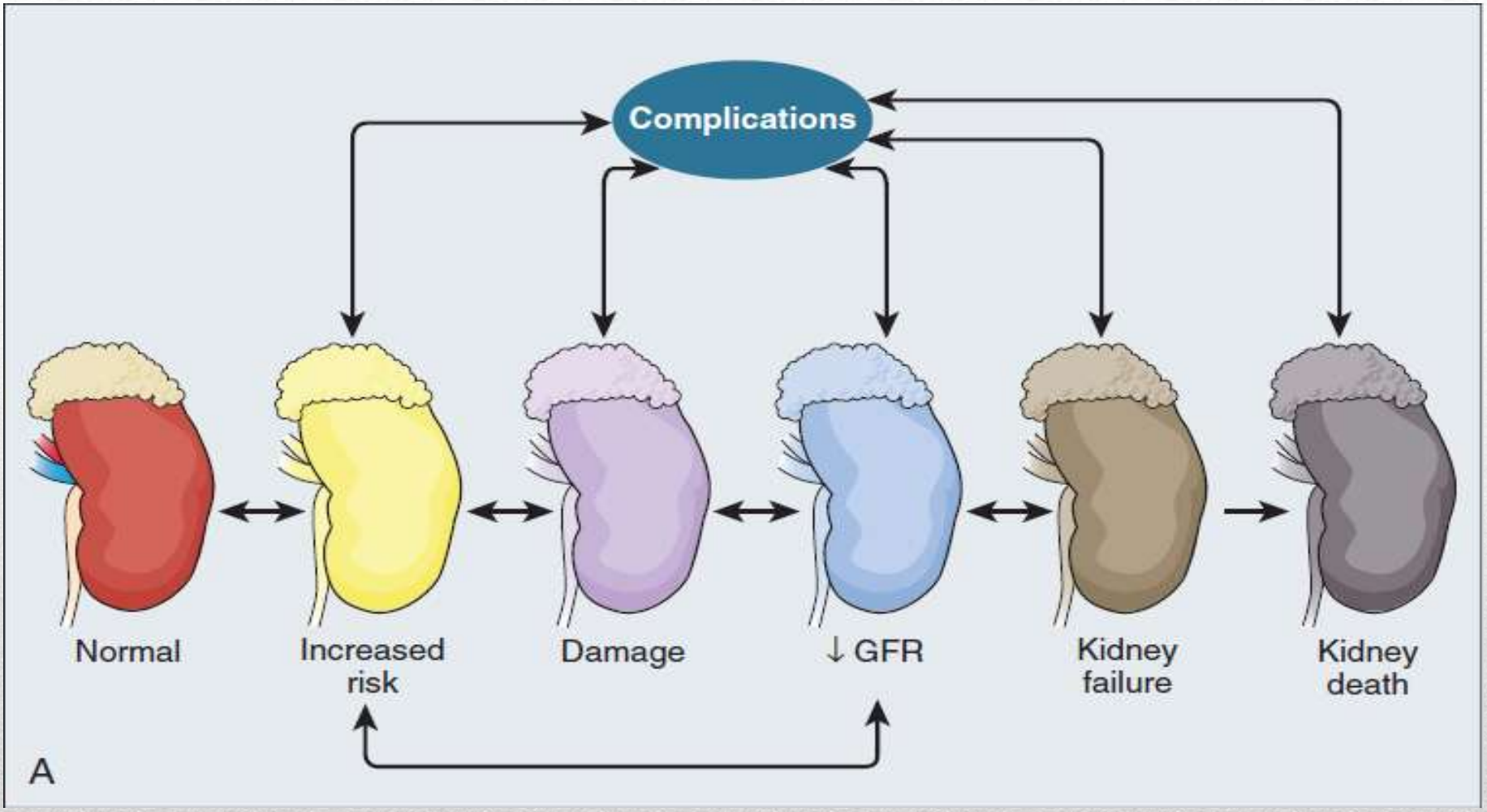



Proposed classification scheme for acute renal failure (ARF)

# RIFLE Classification



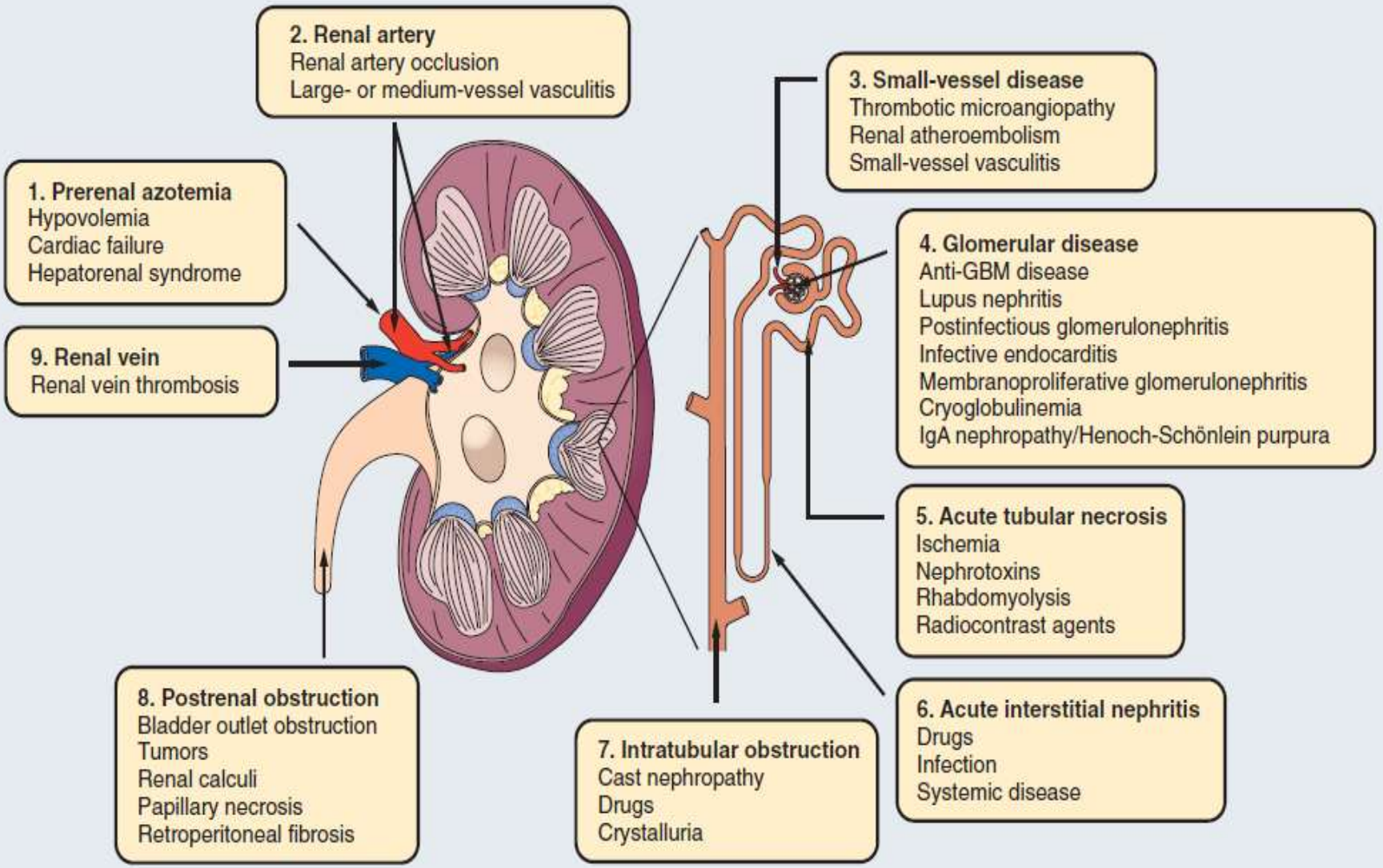

# AKIN Classification



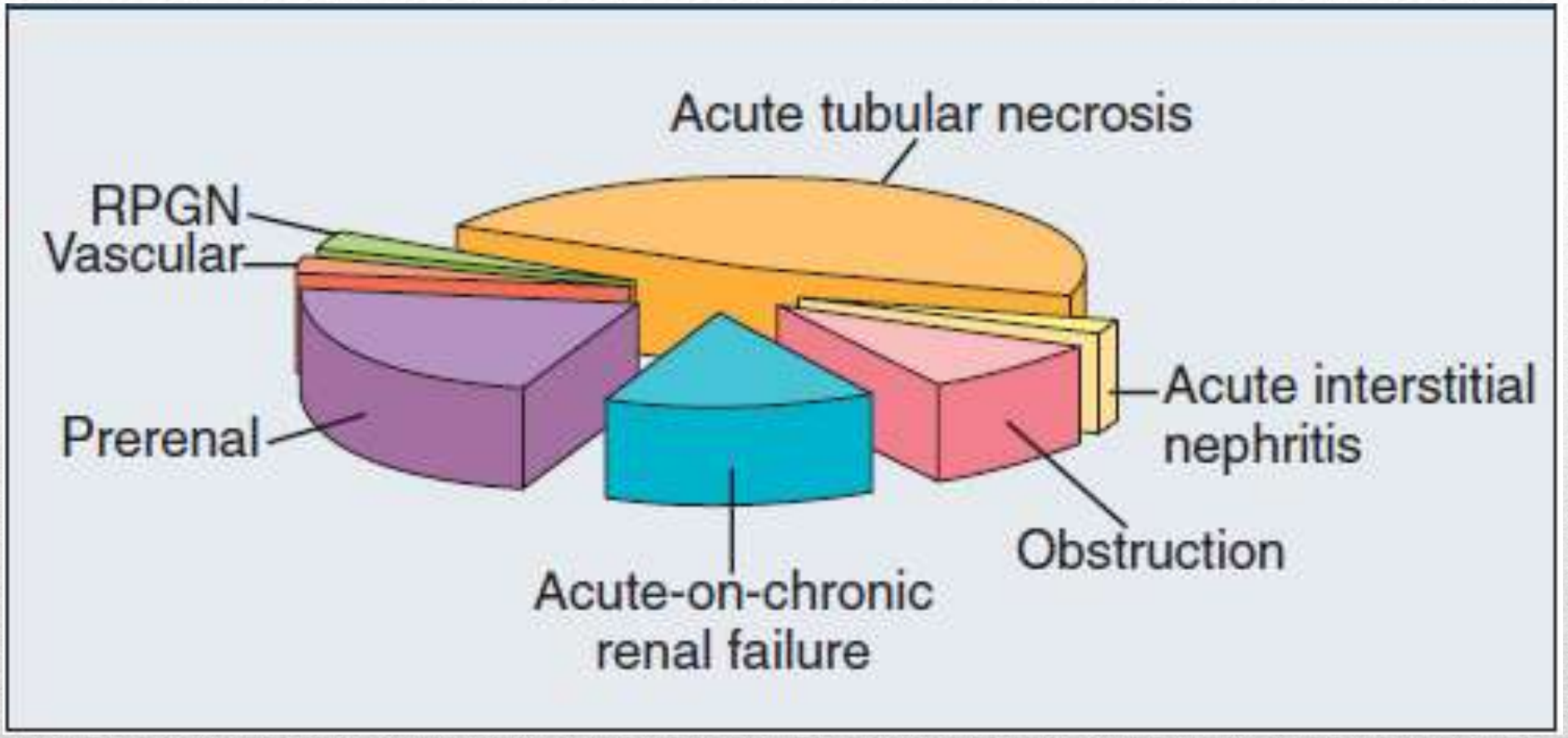

# Kidney Injuiry Continuum

| Patient Factors | Medications and Agents | Procedures |
|---|---|---|
| Pre-existing renal dysfunction | Nonsteroidal anti-inflammatory drugs | Cardiopulmonary bypass procedures |
| Sepsis | | Surgery involving aortic clamp |
| Old age (>75) | Cyclooxgenase-2 inhibitors | Increased intra-abdominal pressure |
| Diabetes | Cyclosporine or tacrolimus | Large arterial catheter placement with risk for atheroembolization |
| Hepatic failure | Angiotensin-converting enzyme inhibitors | Liver transplantation |
| Atherosclerosis | Angiotensin receptor blockers | Kidney transplantation |
| Chronic hypertension | | |
| Perioperative cardiac dysfunction | Use of venous or arterial radiocontrast agents | |
| Hypercalcemia | | |
| Renal artery stenosis | | |

# Major risk factors for AKI


2. Renal artery
Renal artery occlusion
Large- or medium-vessel vasculitis
3. Small-vessel disease
Thrombotic microangiopathy
Renal atheroembolism
Small-vessel vasculitis
1. Prerenal azotemia
Hypovolemia
Cardiac failure
Hepatorenal syndrome
4. Glomerular disease
Anti-GBM disease
Lupus nephritis
Postinfectious glomerulonephritis
Infective endocarditis
Membranoproliferative glomerulonephritis
Cryoglobulinemia
IgA nephropathy/Henoch-Schönlein purpura
9. Renal vein
Renal vein thrombosis
5. Acute tubular necrosis
Ischemia
Nephrotoxins
Rhabdomyolysis
Radiocontrast agents
8. Postrenal obstruction
Bladder outlet obstruction
Tumors
Renal calculi
Papillary necrosis
Retroperitoneal fibrosis
7. Intratubular obstruction
Cast nephropathy
Drugs
Crystalluria
6. Acute interstitial nephritis
Drugs
Infection
Systemic disease

# Etiology




# Causes of AKI in Hospital

# Prerenal AKI

## ECF volume depletion

- GIT losses: diarrhea, vomiting, prolonged nasogastric drainage
- Renal losses: diuretics, osmotic diuresis in hyperglycemia
- Dermal losses: burns, extensive sweating
- Third space loss: acute pancreatitis, muscle trauma

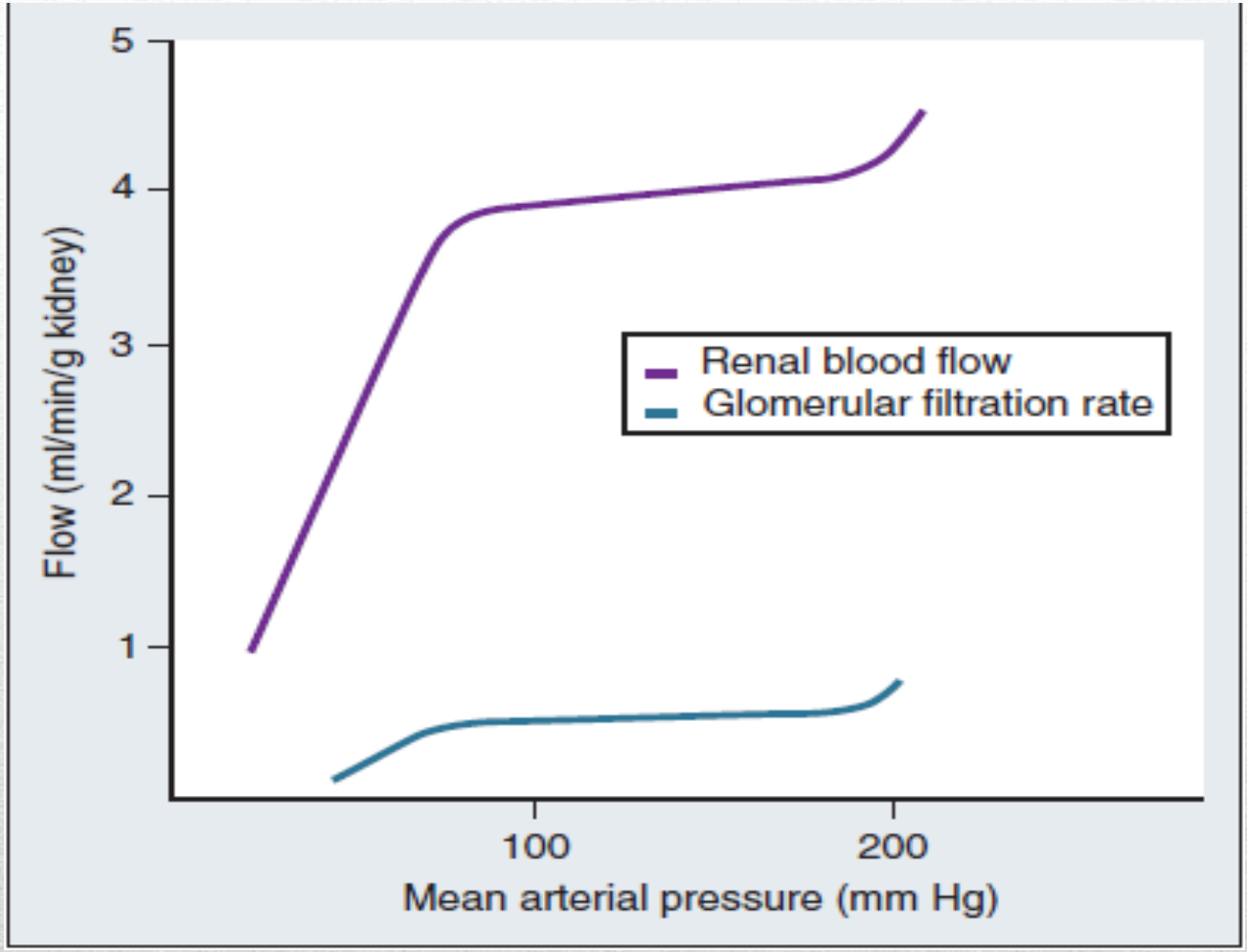
# Prerenal AKI

## Normal or increased ECF fluid

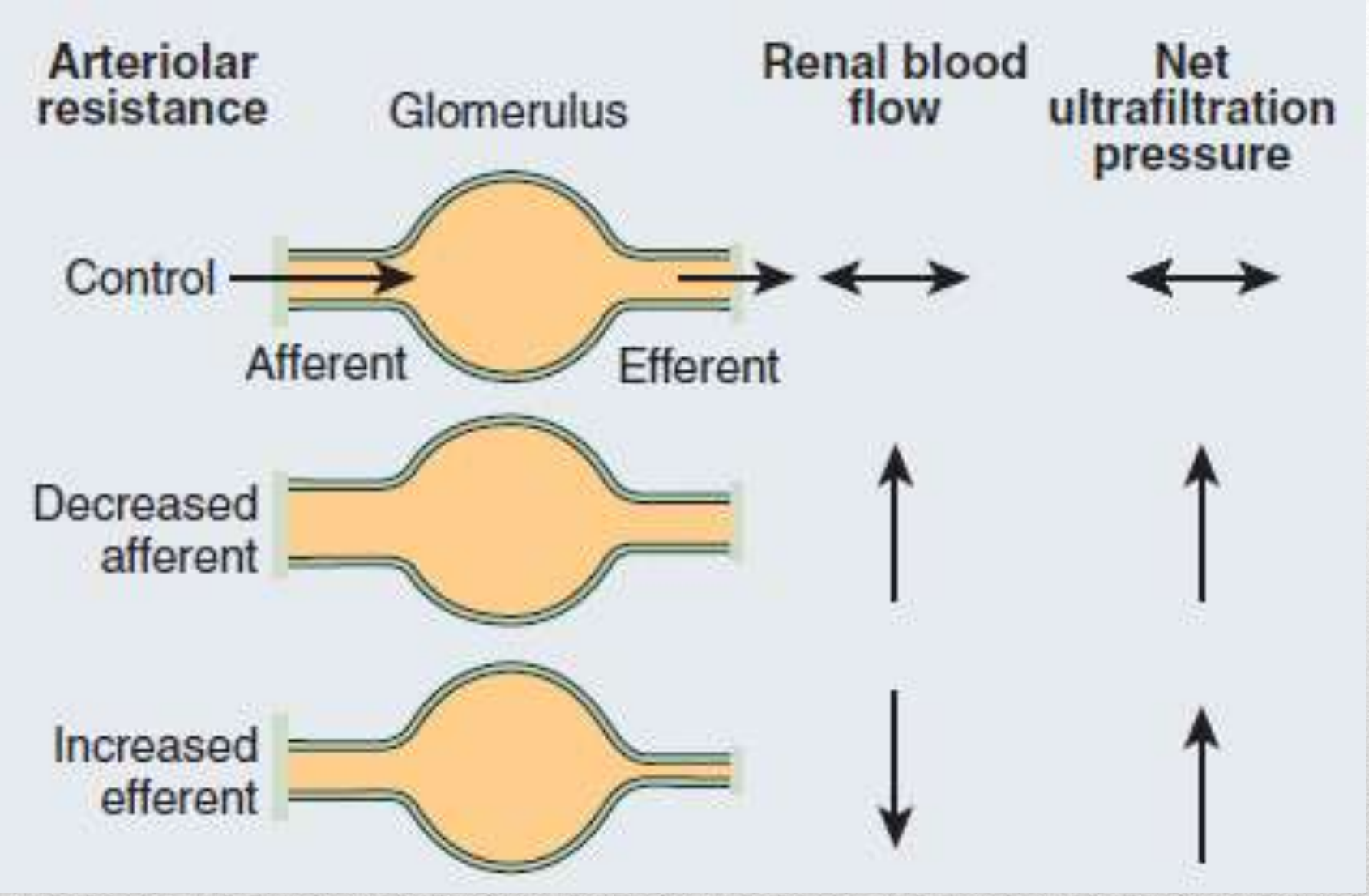
- Decreased COP: heart failure
- Systemic VD with redistribution of COP to extrarenal vascular beds: sepsis, liver cirrhosis.

## Hyperoncotic state

- Mannitol, dextran and protein



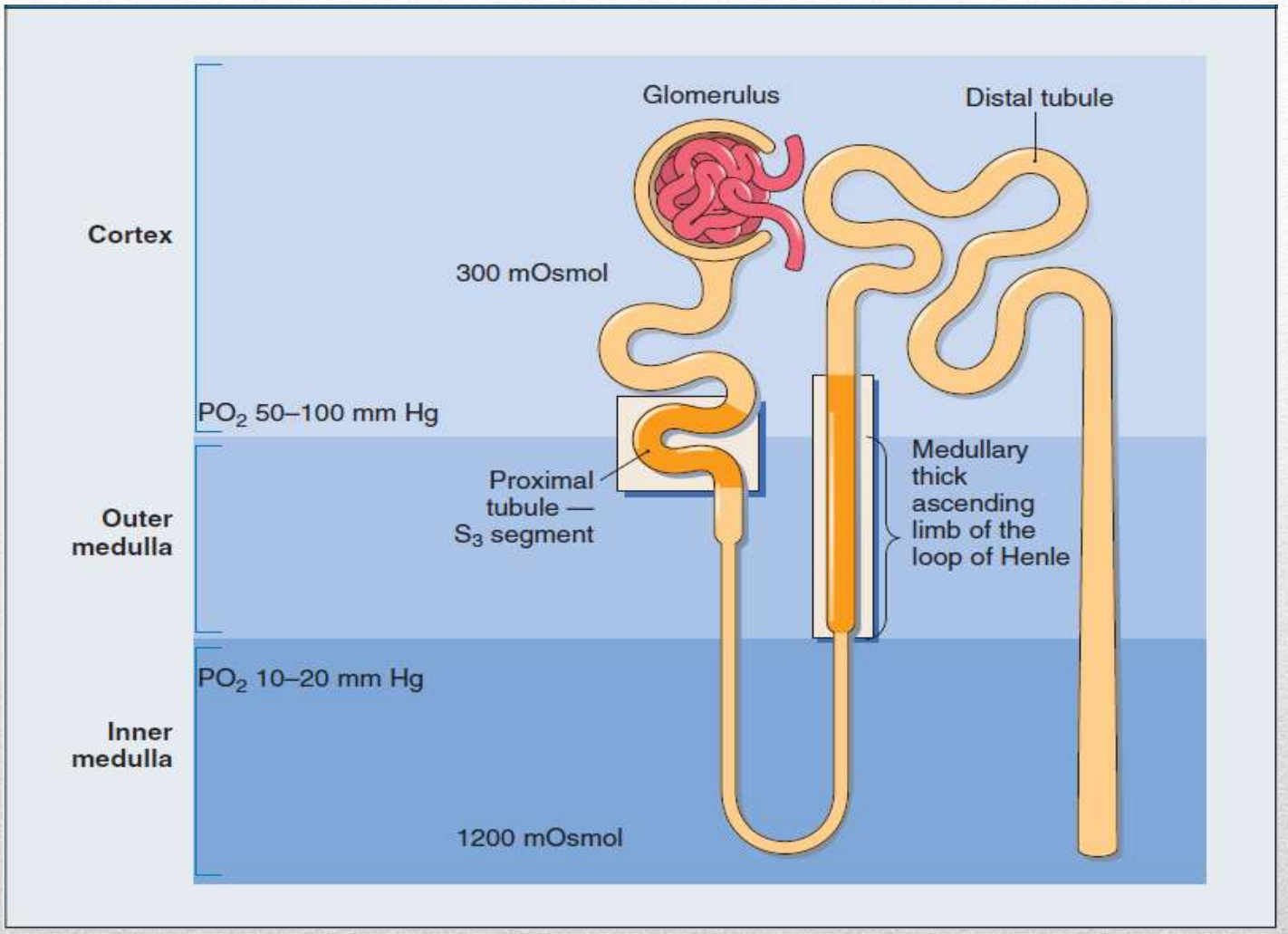

# Pathophysiology of prerenal AKI


Arteriolar resistance
Glomerulus
Renal blood flow
Net ultrafiltration pressure
Control
Afferent
Efferent
Decreased afferent
Increased efferent

| | Afferent Arteriolar Resistance | Efferent Arteriolar Resistance | Renal Blood Flow | Net Ultrafiltration Pressure | $K_f$ | GFR |
|---|---|---|---|---|---|---|
| Renal sympathetic nerves | ↑↑ | ↑ | ↓ | ↓ | ↓ | ↓ |
| Epinephrine | ↑ | ↑ | ↓ | → | ? | ↓ |
| Adenosine | ↑ | → | ↓ | ↓ | ? | ↓ |
| Cyclosporine | ↑ | → | ↓ | ↓ | ? | ↓ |
| NSAIDs | ↑↑ | ↑ | ↓ | ↓ | ? | ↓ |
| Angiotensin II | ↑ | ↑↑ | ↓ | ↑ | ↓ | ↓→ |
| Endothelin 1 | ↑ | ↑↑ | ↓ | ↑ | ↓ | ↓ |
| High-protein diet | ↓ | → | ↑ | ↑ | → | ↑ |
| Nitric oxide | ↓ | ↓ | ↑ | ? | ↑ | ↑(?) |
| Atrial natriuretic peptide (high dose) | ↓ | → | ↑ | ↑ | ↑ | ↑ |
| Prostaglandins $E_2/I_2$ | ↓ | ↓(?) | ↑ | ↑ | ? | ↑ |
| Calcium channel blockers | ↓ | → | ↑ | ↑ | ? | ↑ |
| ACE inhibitors/angiotensin receptor blockers | ↓ | ↓↓ | ↑ | ↓ | ↑ | ?* |

# ATN

- Ischemic
- Toxic:
  - Endogenous: hemoglobinuria and myoglobinuria
  - Exogenous: aminoglycosides and radiocontrast agents

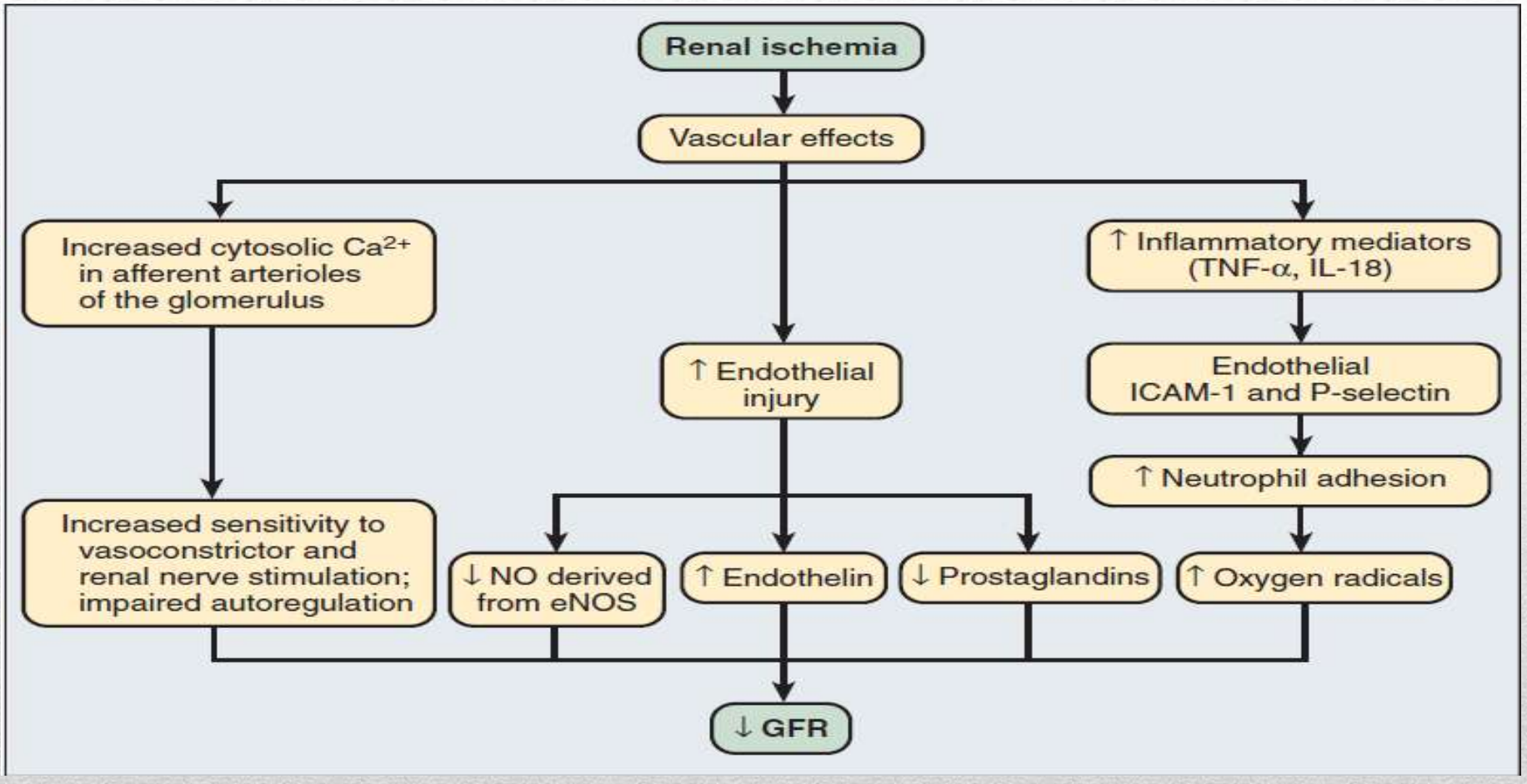



# Pathophysiology of ATN

# Pathophysiology of ATN

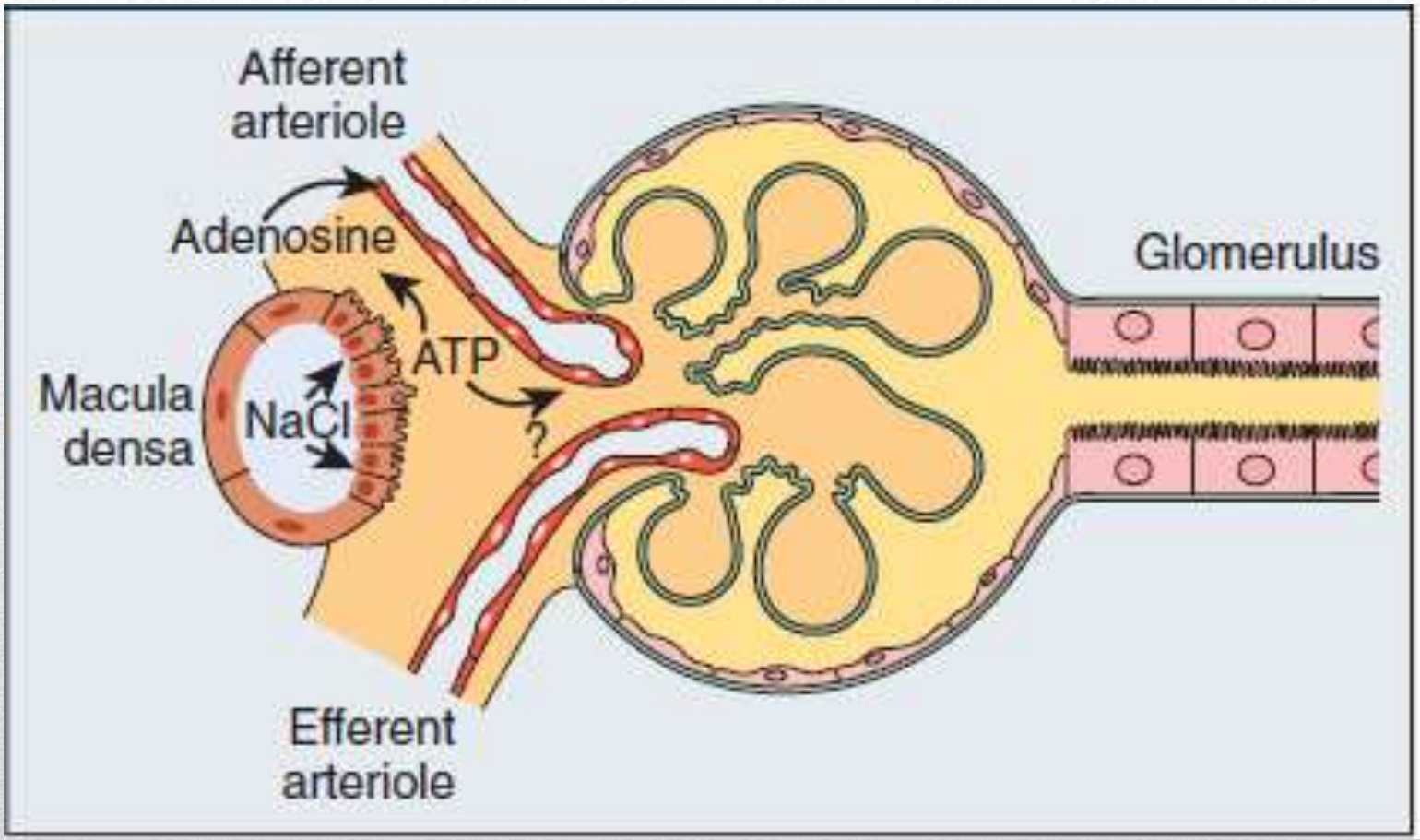
## 1. Impaired Renal Autoregulation

# 2. Intrarenal vasoconstriction




# Pathophysiology of ATN

# 3. Tubuloglomerular feedback

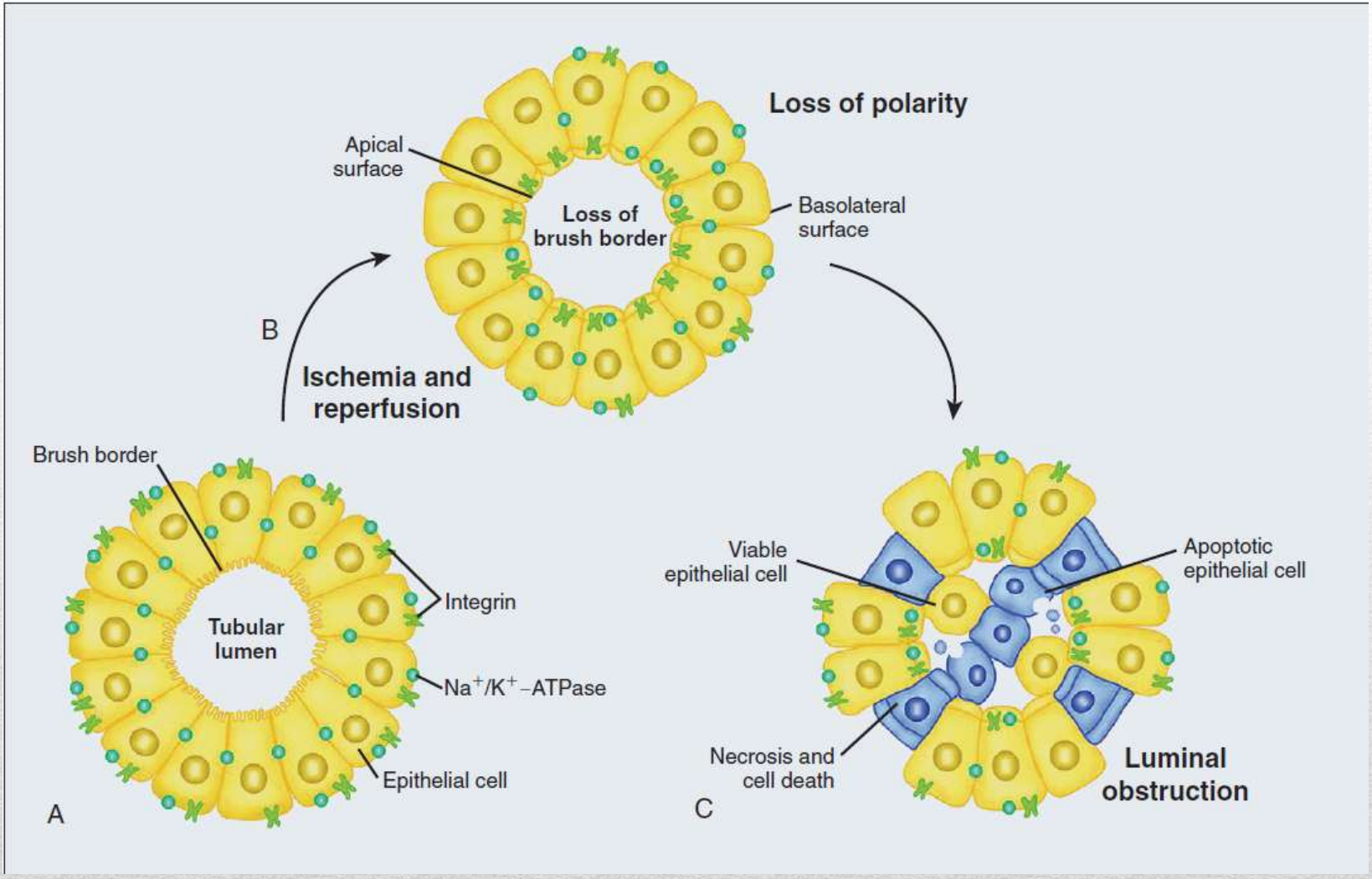



# Pathophysiology of ATN

# 4. Inflammatory factors

- Proinflammatory cytokines: TNF-α,  IL-6 and IL-1b
- Chemokines: MCP-1, IL-8, RANTES
- Innate immune systems: complement system and TLR2 and TLR4.
- Activation of complement
- T lymphocytes

# Pathophysiology of ATN




# Pathophysiology of ATN

# Postrenal AKI

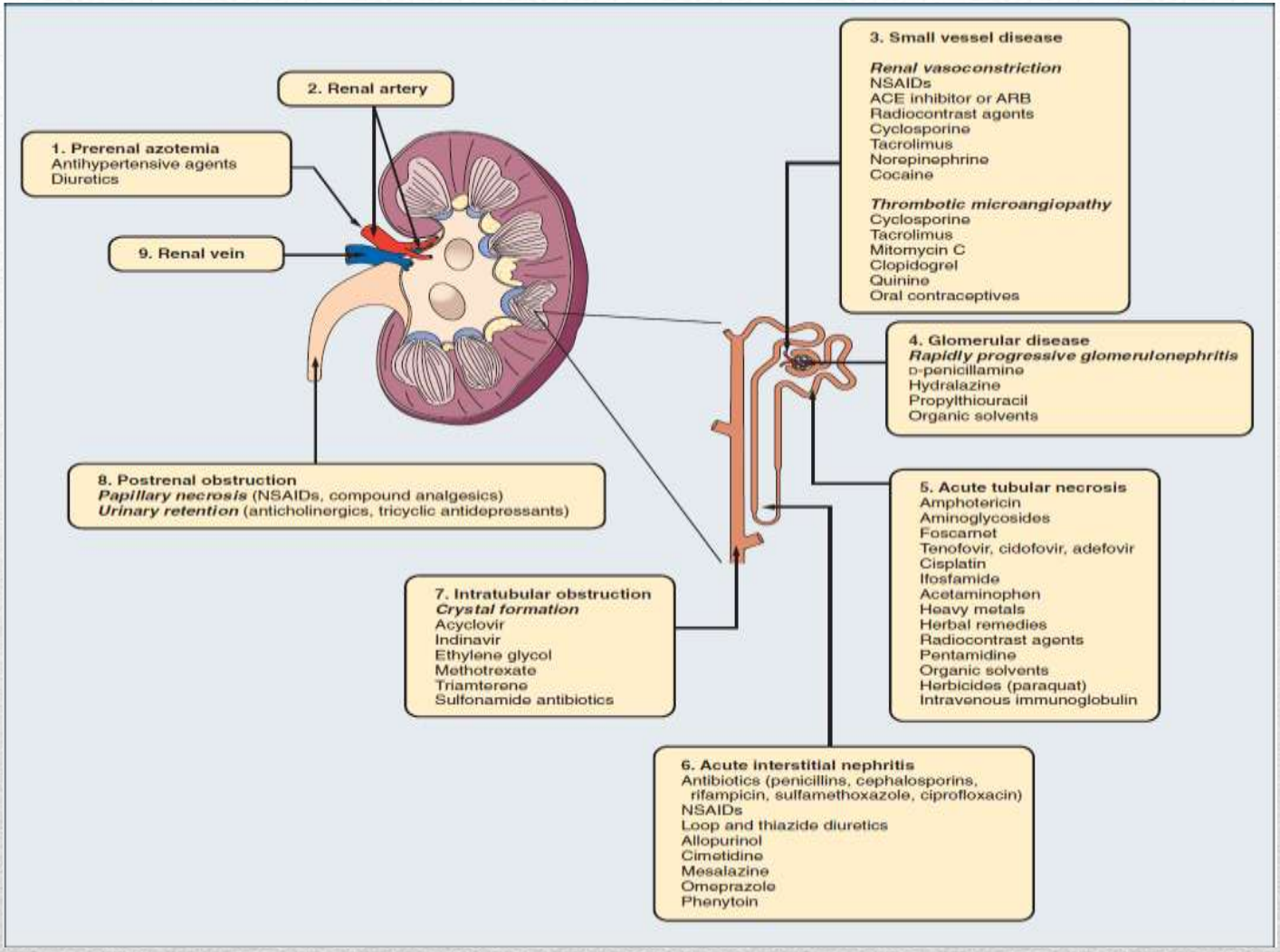
## Intrarenal (tubular)

- Insoluble crystals (phosphate, methotrexate, acyclovir, sulfonamides, indinavir, uric acid, triamterene, oxalic acid)
- Protein (hemoglobin, myoglobin, paraprotein)

## Extrarenal

- Obstruction of renal pelvis, ureters, bladder, or urethra

# Specific Categories of AKI



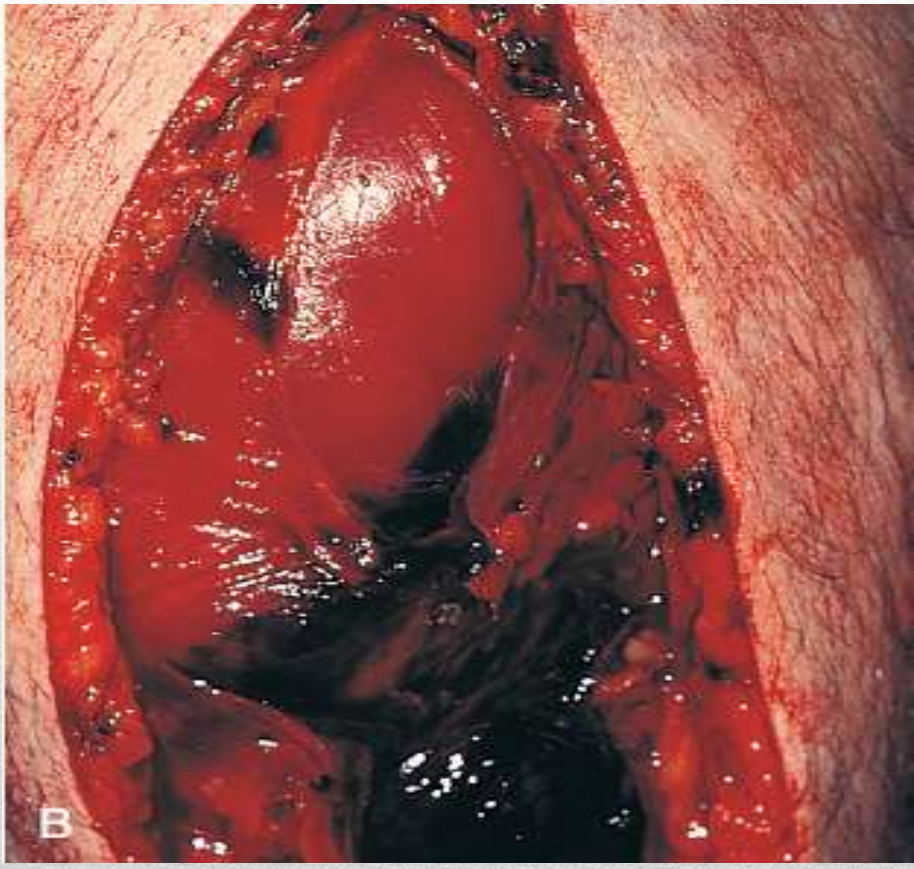

# Nephrotoxic agents & AKI

# 1. Rhabdomyolysis

| | |
|---|---|
| Muscle injury/ischemia | Trauma, pressure necrosis, electric shock, burns, acute vascular disease |
| Myofiber exhaustion | Seizures, excessive exercise, heat exhaustion |
| Toxins | Alcohol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, snakebite |
| Drugs | Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics |
| Electrolyte disorders | Hypophosphatemia, hypokalemia, excess water shifts (hyperosmolality) |
| Infections | Viral (influenza, HIV, Coxsackievirus, Epstein-Barr virus), bacterial (*Legionella*, *Francisella*, *Streptococcus pneumoniae*, *Salmonella*, *Staphylococcus aureus*) |
| Familial | McArdle's disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia |
| Other | Hypothyroidism, polymyositis, dermatomyositis |

# Heme Pigment Nephropathy

# Compartment Syndrome

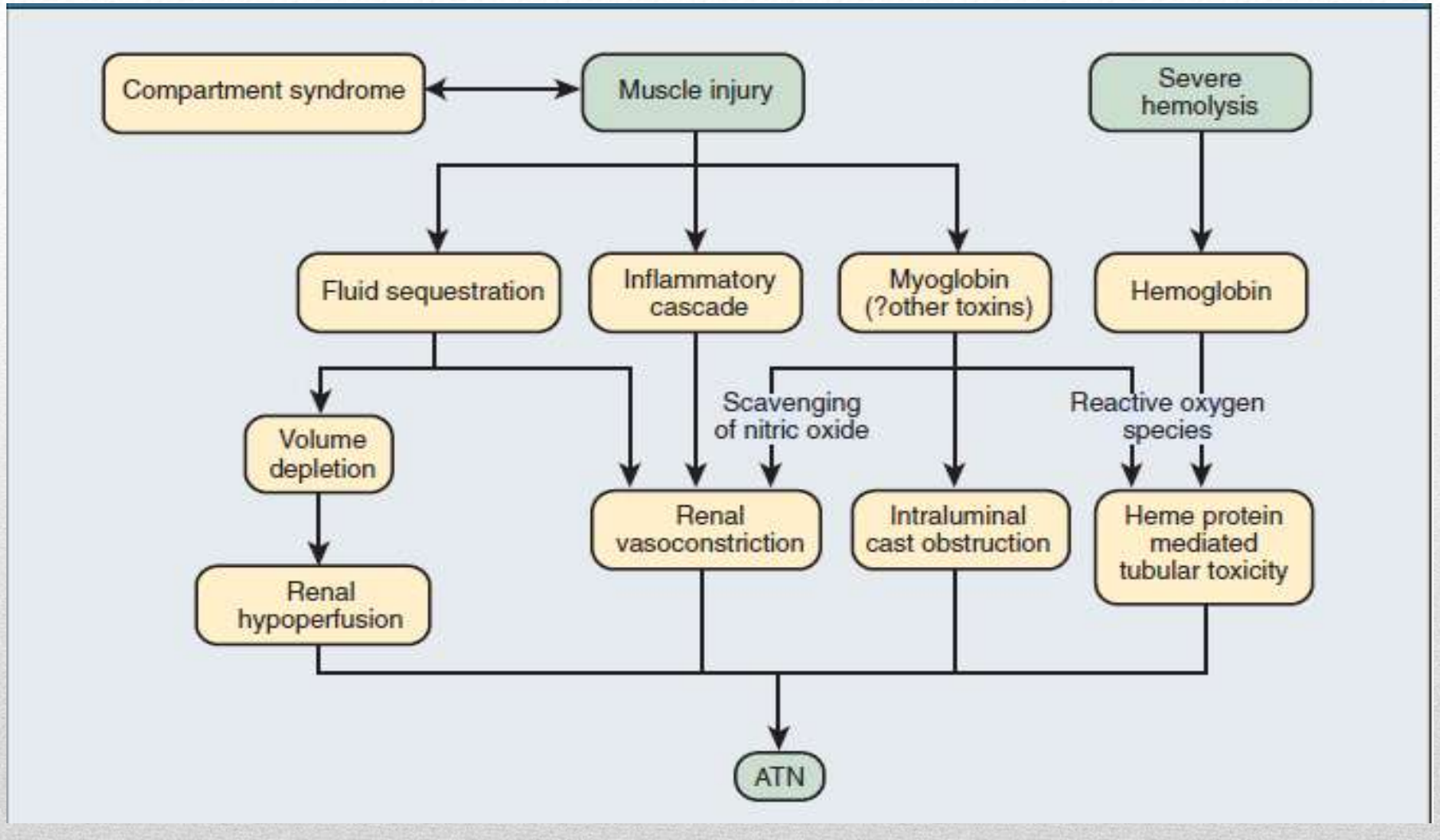




# Heme Pigment Nephropathy

# 2. Hemoglobinuria

- Incompatible blood transfusion
- Autoimmune hemolytic anemia
- Malaria (blackwater fever),
- Glucose-6-phosphate dehydrogenase deficiency
- Paroxysmal nocturnal hemoglobinuria
- March hemoglobinuria
- Toxins: dapsone, venoms

# Heme Pigment Nephropathy




# Pathophysiology of Heme Pigment Nephropathy

# Risk factors

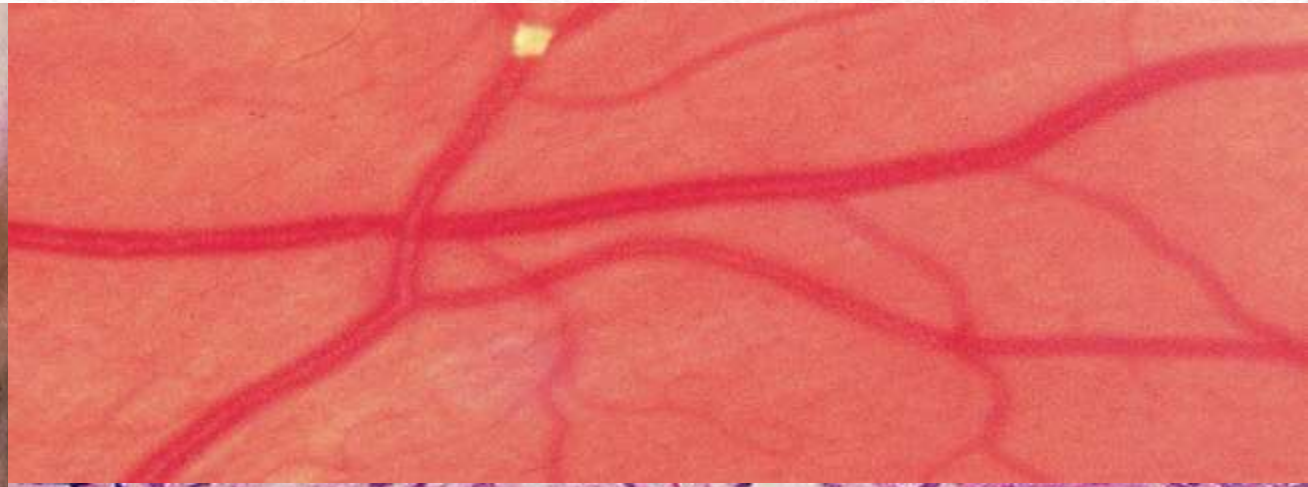
- Creat. > 1.5 mg/dl
- Systolic BP < 80 mmHg for > 1 hr or need for inotropic support
- Use of IABP
- Heart failure (NYHA class 3 or 4)
- History of pulmonary edema
- Volume of contrast > 100 ml

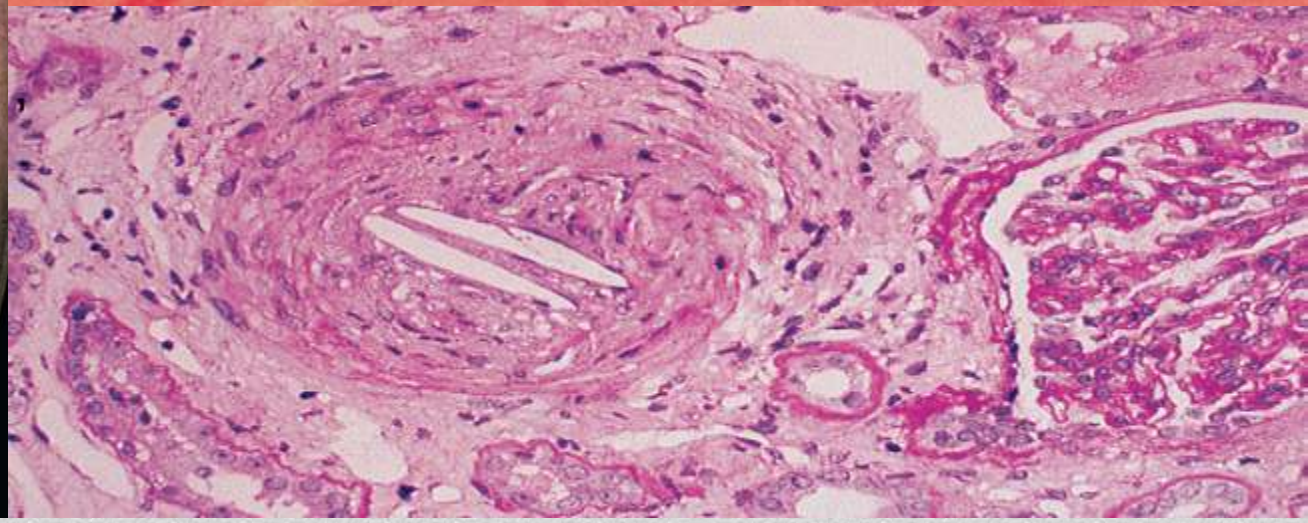
# Contrast nephropathy

- Age > 75 years
- DM
- Anemia, blood loss
- High osmolar contrast agent
- Volume depletion
- Concurrent nephrotoxic agents: NSAIDs or ACE inhibitors.+

# Pathogenesis

- Medullary hypoxia: renal VC
- Direct tubular epithelial cell toxicity: ROS





# Atheroembolic renal disease

# The Thrombotic microangiopathies

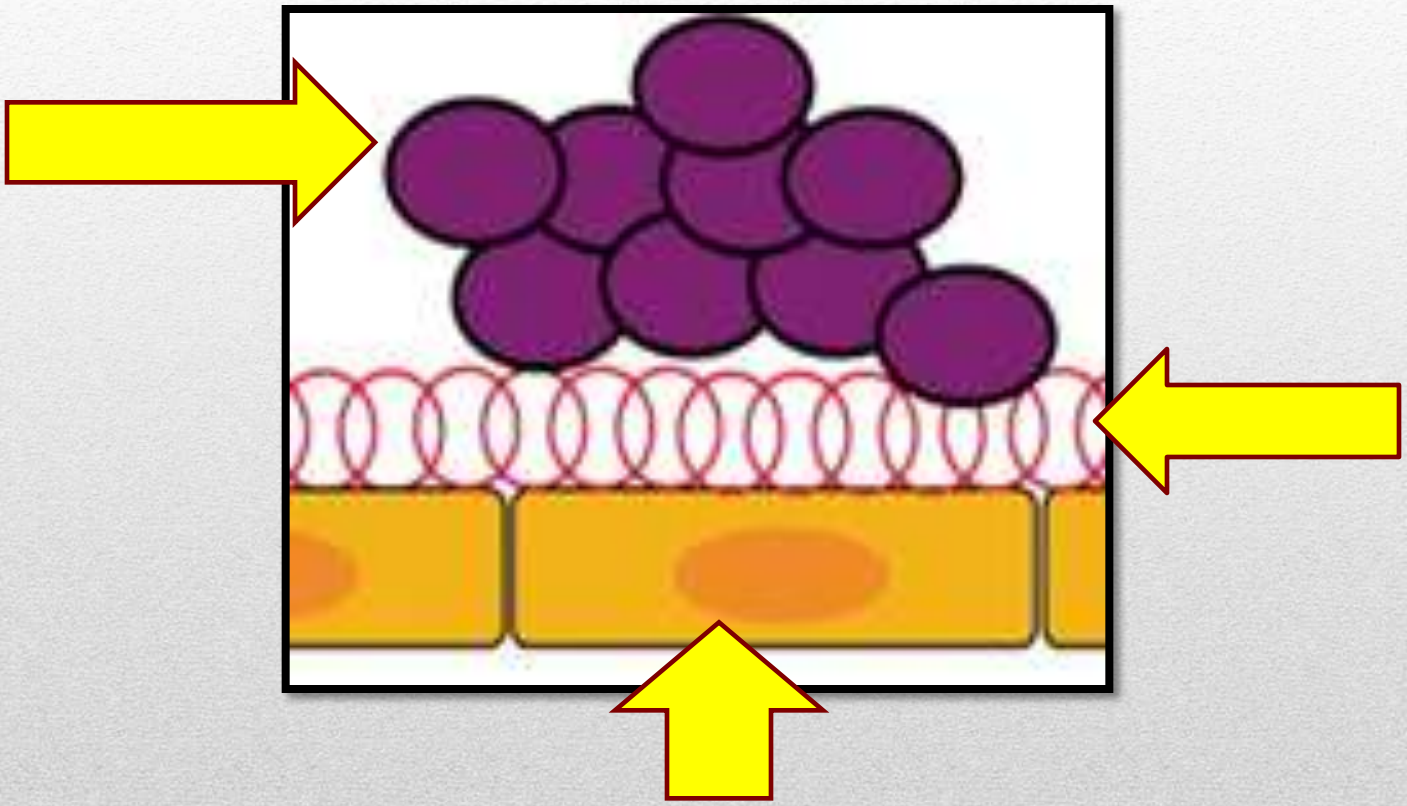
are microvascular occlusive disorders characterized by

- (1)Systemic and or intrarenal aggregation of platelets,
- (2)thrombocytopenia
- (3)mechanical injury to erythrocytes

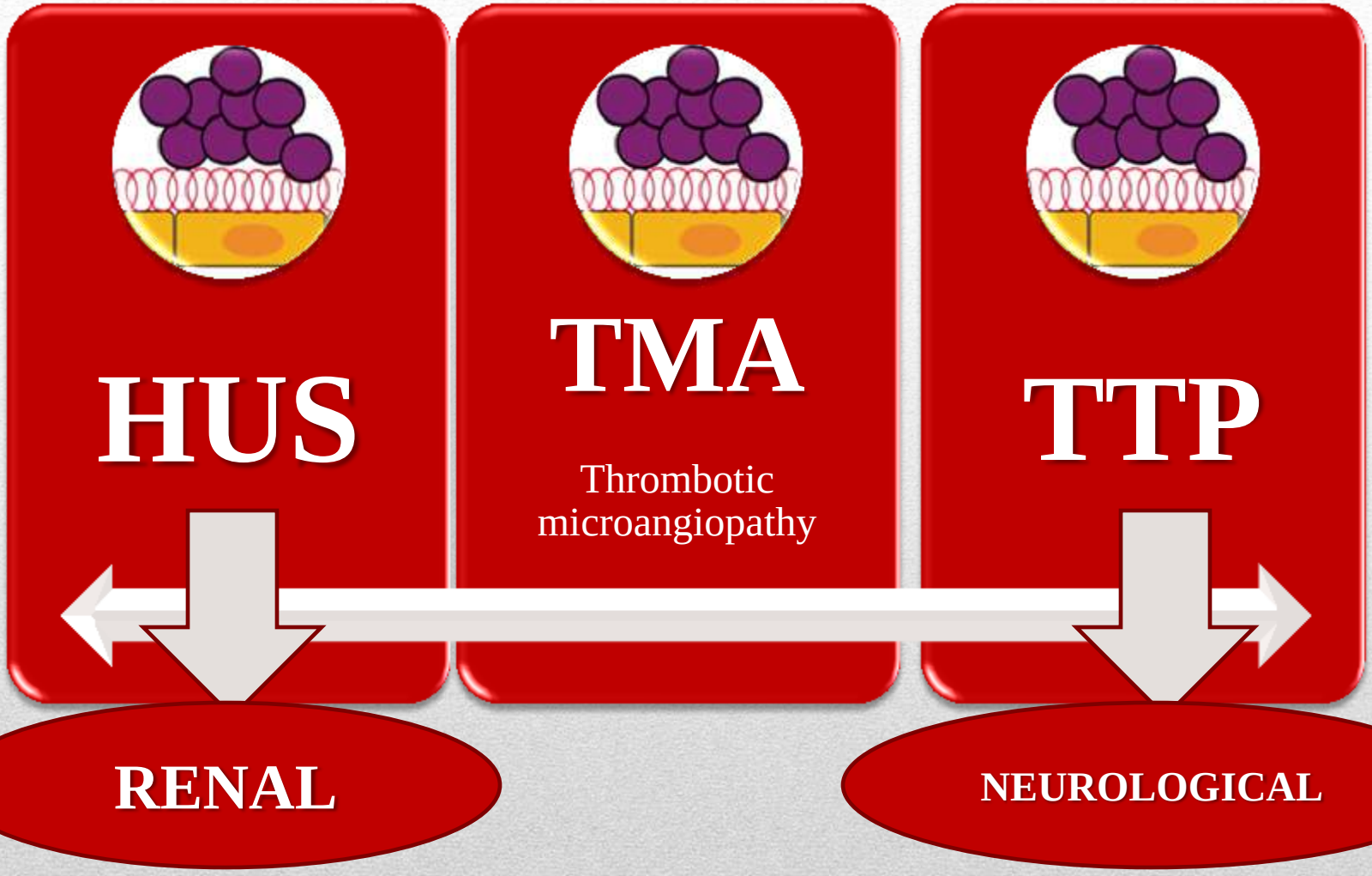
# Thrombotic Microangiopathy

# THE CRIMINALS IN THE DISEASE

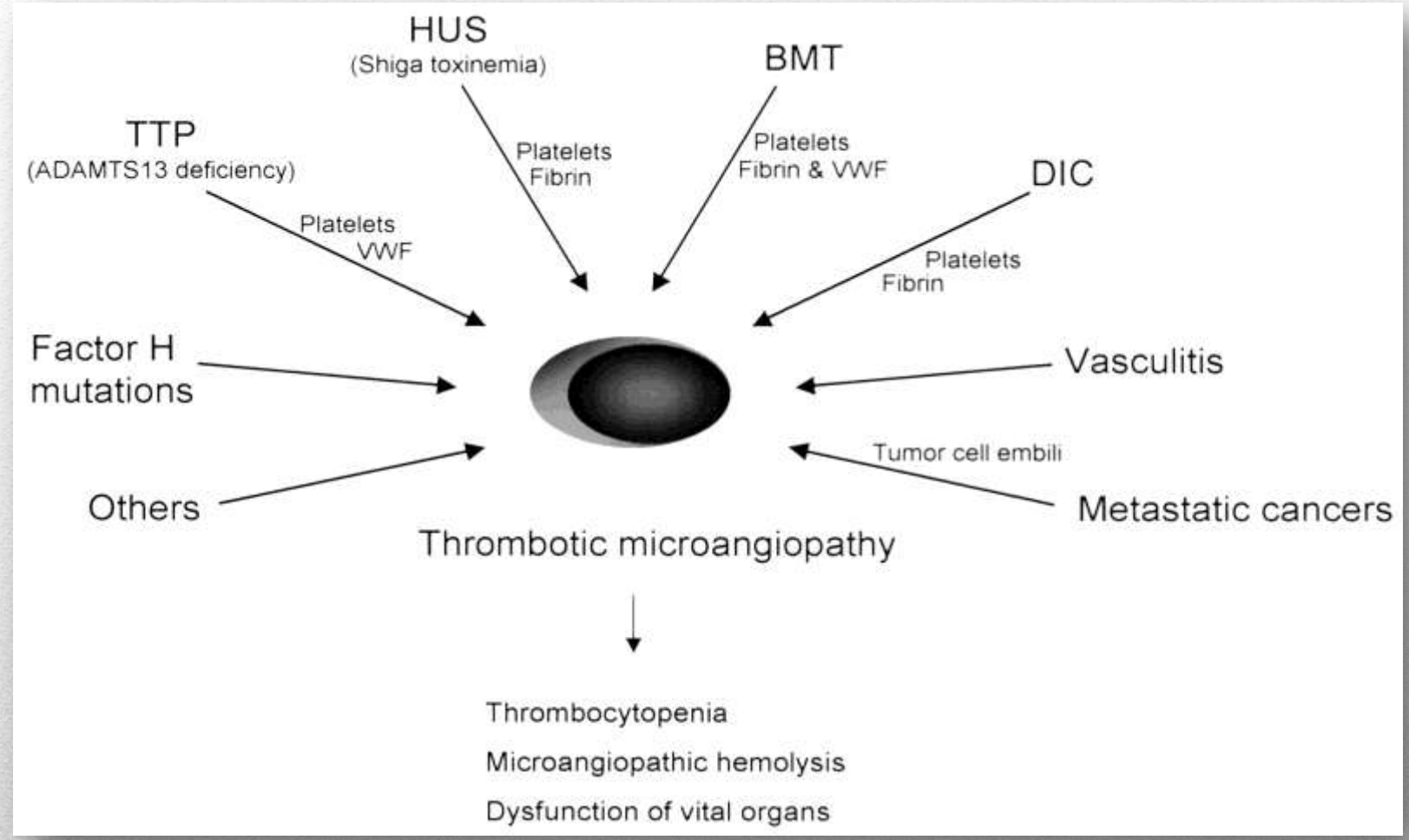
## ALL ARE PARTNERS



# Thrombotic Microangiopathy




# Thrombotic Microangiopathy




Tsai H JASN 2003;14:1072-1081

# Thrombotic Microangiopathy

# Multiorgan failure

- Hypotension
- Impaired renal perfusion
- Inflammatory mediators:
- Nephrotoxic agents

# Abdominal Compartment Syndrome

- ↑intra-abdominal pressures (>20 mm Hg):
  - Trauma.
  - After abdominal surgery
  - Massive fluid resuscitation

# Pregnancy related AKI

- Hyperemesis graviderum
- Severe hge during delivery
- Sepsis
- PET & HELLP syndrome
- NSAIDs

| | |
|---|---|
| Systemic vasculitis | Anti-GBM disease (Goodpasture's)<br>ANCA associated<br>• Wegener's granulomatosis<br>• Microscopic polyarteritis<br>• Churg-Strauss syndrome<br>• Drugs (penicillamine, hydralazine, propylthiouracil)<br>Immune complex disease<br>• Lupus erythematosus<br>• Henoch-Schönlein purpura<br>• Mixed cryoglobulinemia<br>• Rheumatoid vasculitis |
| Infection | Severe bacterial pneumonia; postinfectious glomerulonephritis; *Legionella;* hantavirus; opportunistic infection in immunocompromised patients; infective endocarditis |
| Pulmonary edema and AKI | Volume overload; severe left ventricular failure |
| Multiorgan failure | Acute respiratory distress syndrome and AKI |
| Other | Paraquat poisoning; renal vein or IVC thrombosis with pulmonary emboli |

# Pulmonary-Renal Syndromes

| | |
|---|---|
| Prerenal uremia | Diuretic use, gastrointestinal loss, peritoneal aspiration, hypoalbuminemia |
| Hepatorenal syndrome | |
| Acute tubular necrosis | Hyperbilirubinemia, sepsis, toxic shock syndrome |
| Drugs | Acetaminophen (paracetamol), NSAIDs, tetracycline, rifampicin, isoniazid, anesthetic agents, sulfonamides, allopurinol, methotrexate |
| Infections | Hepatitis C and cryoglobulinemia, hepatitis B and polyarteritis nodosa, leptospirosis, hantavirus, Epstein-Barr virus, gram-negative sepsis, spontaneous bacterial peritonitis |
| Other | Papillary necrosis and obstruction, inhalation of chlorinated hydrocarbons, mushroom poisoning (*Amanita phalloides*) |

# AKI in liver diseases

| | |
|---|---|
| Prerenal | Nausea and vomiting, hypercalcemia, cardiomyopathy secondary to chemotherapy |
| Vascular | Thrombotic microangiopathy (adenocarcinoma of stomach, pancreas, prostate; radiation nephropathy), renal vein thrombosis secondary to hypercoagulability, disseminated intravascular coagulation (acute promyelocytic leukemia) |
| Glomerular | Rapidly progressive glomerulonephritis |
| Acute tubular necrosis | Sepsis and antibiotic nephrotoxicity, hypercalcemia |
| Malignant infiltration | Lymphoma, acute lymphoblastic leukemia |
| Intraluminal obstruction | Tumor lysis syndrome, cast nephropathy |
| Postrenal obstruction | Transitional cell carcinoma of the ureters/bladder, extrinsic ureteral compression (tumor, nodes, retroperitoneal fibrosis) |
| Chemotherapeutic agents | |
| Tubular toxicity | Cisplatin, ifosfamide, plicamycin (mithramycin); 5-fluorouracil, thioguanine (6-thioguanine), cytarabine |
| Thrombotic microangiopathy | Mitomycin C, bleomycin, cisplatin, calcineurin inhibitors |
| Other mechanisms | Capillary leak syndrome (IL-2 therapy), acute interstitial nephritis (interferon-α), intraluminal obstruction (methotrexate) |

# AKI with cancer

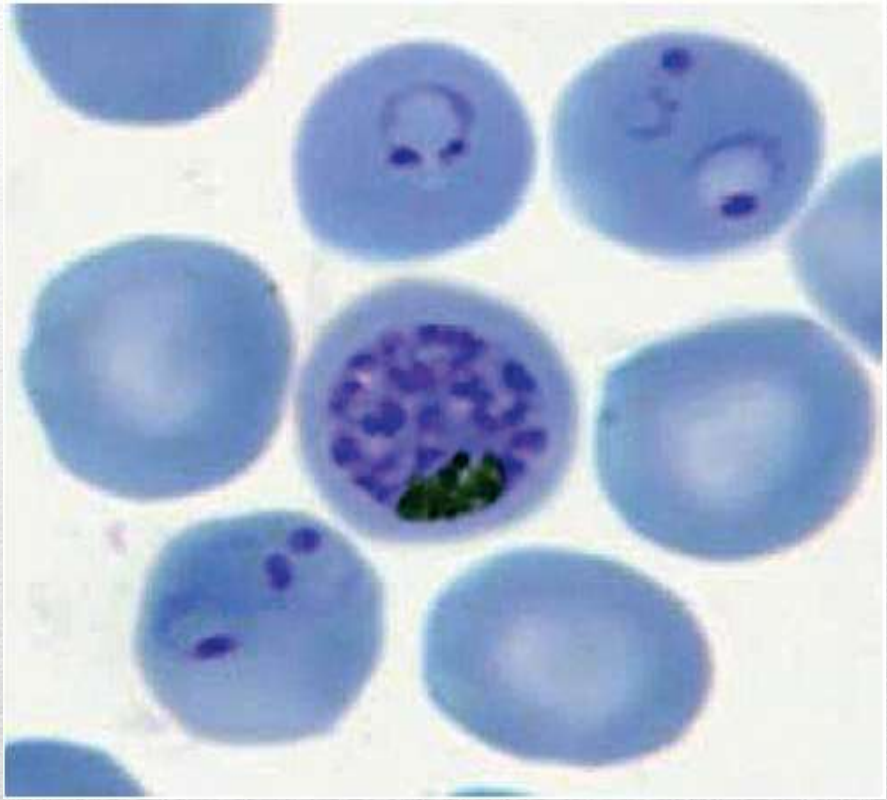
Russell's Viper Snake

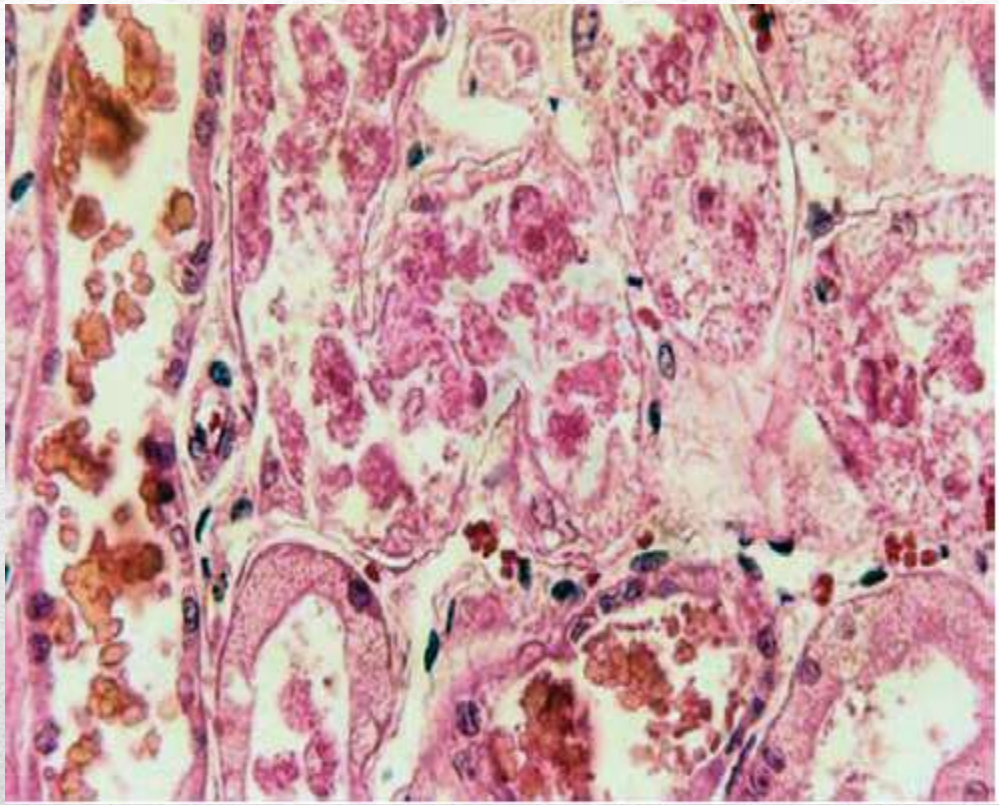
# AKI in tropics

Lonomia obliqua caterpillars

Loxosceles spider


# AKI in tropics





# AKI in tropics

# Thank You